

DIABETES AND THE PREGNANCY

CHALLENGES FOR THE MOTHER AND CHILD A LITERATURE REVIEW



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Abstract

Background

Previously, diabetes was a contraindication to pregnancy, and few live children were born and raised by mothers with diabetes. The current situation is much different, and women with diabetes are no longer discouraged to get pregnant. There are however still many challenges found in pregnancies complicated by diabetes. Improvements have been made, but there are still a higher rate of pre-eclampsia, stillbirths, perinatal death and infant death amongst pregnancies complicated by diabetes. In addition to this, there is also a higher rate of macrosomia and congenital birth defects, such as cardiovascular and neural spine defects.

The aim of this project is to look at the obstetric situation for women living with diabetes today, with regard to the kind of preparations that have to be made prior to conception, major health risks during pregnancy for mother and fetus, and the outcomes of the babies and mothers. And lastly, to identify potential areas for improvement of outcome (defined as live healthy newborn, 28 days after delivery).

Methods

The project method is a non-systematic literature review searching the databases PubMed, McMaster PLUS and Cochrane library. The search was limited to original articles and reviews published in English.

Search words: diabetes, pregnan*, risk, future, treatment

Findings

The risk factors in a pregnancy complicated by diabetes can be divided into different groups dependent on what time in the pregnancy it will lead to adverse outcomes and whether it affects the mother or the baby. The complications known today are congenital malformations, death of fetus/infant, pre-eclampsia, preterm birth, macrosomia/large for gestational age baby, microvascular complications for mother and increased risk for developing diabetes and obesity later in life for mothers with gestational diabetes and offspring of parents with diabetes.

Discussion

The complications for mother and child in pregnancy complicated by diabetes are mainly due to hyperglycemia. To predict the outcome of the pregnancy, one has to look at the degree of hyperglycemia, and at what time in the pregnancy this occurs. It is obvious that to maintain strict glycemic control is a major challenge for those involved.

Conclusion

There are still many challenges in the pregnancy care of women with diabetes. The mechanisms behind malformations, premature birth, preeclampsia and stillbirth are still not fully understood, but all of the challenges are related to suboptimal glycemic control in the pregnancy.

To promote healthy lifestyle pre-conceptionally is of utmost importance.

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1.0 Abbreviations:

ADA: American Diabetes Association

BNP: Brain Natriuretic Peptide

CEMACH: Confidential Enquiry into Mother and Child Health

EPO: Erythropoietin

FFA: Free Fatty Acids

GDM: Gestational Diabetes Mellitus

HAPO: Hyperglycemia and Adverse Pregnancy Outcome study

HbA1c: Glycosylated hemoglobin

IADPSG: International Association of Diabetes and Pregnancy Study Groups

ISPAD: International Society for Pediatric and Adolescent Diabetes

LGA: Large for Gestational Age

MBRN: Medical Birth Registry of Norway

NCDR: Norwegian Childhood Diabetes Registry

NGF: Norwegian Society for Gynecology

NICE: National Institute for health and Clinical Excellence

OGTT: Oral Glucose Tolerance Test

PG: Plasma Glucose

PGDM: Pregestational Diabetes Mellitus

pro-BNP: pro-Brain Natriuretic Peptide

RDS: Respiratory Distress Syndrome

SGA: Small for Gestational Age

T1D: Type 1 Diabetes

T2D: Type 2 Diabetes

2.0 Literature review

2.1 Background:

Insulin did not become available until the early 1920s, and most subjects with type 1 diabetes (T1D) only lived a few months following the onset of the disease [1]. Diabetic ketoacidosis occurred frequently, so maternal death occurred commonly in pregnancies complicated by diabetes [2]. Not until the mid-1930s was the association of birth defects with diabetic pregnancy recognized, when use of insulin allowed the focus of clinical care to shift from maternal survival to neonatal outcome.

The American pioneer in diabetes care of pregnant women, Pricilla White wrote in 1936, “Congenital defects [including heart defects, gastrointestinal atresia, microcephaly, and achondroplasia] are beyond our therapeutic control and are, we believe, related to a disease which is genetic in origin” [3, 4]. In 1949 she wrote the article ‘Pregnancy complicating diabetes’, published in American Journal of Medicine [3]. Here she first introduced the system later known as ‘White’s Classification Index of Diabetic Pregnancies’. She classified the patient after their level of risk determined by age at onset, duration, presence of atherosclerotic vascular disease and renal complications. Later she added proliferative retinopathy as risk factor. The index was used to determine the outcome of the pregnancy and to give appropriate therapy and follow-up. This system became widely used throughout the world.

As progression in diabetic care were made, new medical challenges arised, and a whole new patient group were born; the offspring of mothers with diabetes. The two major improvements that lead to this was the recognition that improved control of maternal diabetes reduced morbidity and mortality of both the mother and the fetus. The other was the discovery of surfactant to reduce parinatal mortality from respiratory distress syndrome (RDS)[4]. Offspring of mothers with diabetes had increased risk of RDS both because there is an increased risk of pre-term birth and fetal insulin inhibits lung maturation [5].

RDS was largely treatable by the 1980s, and then major cause of neonatal mortality became congenital malformations [4]. As the malformations are to some extent caused by lack of glucose control in early pregnancy, the focus shifted again to pre-conceptional counselling and care.

It is also a well known fact that thyroid dysfunction is prevalent amongst women with diabetes[6], and this may further complicate the outcome for the infant in the form of cerebral dysfunction.

The increasing incidence of Type 2 Diabetes (T2D) is a major challenge for the future. In Oslo T2D leads to more congenital malformations and complications in pregnancy than T1D[7].

Table 1:

Modified White's Classification Index of Diabetic Pregnancies:
<p>There are 2 classes of gestational diabetes (diabetes which began during pregnancy):</p> <ul style="list-style-type: none">• Class A₁: gestational diabetes; diet controlled• *Class A₂: gestational diabetes; medication controlled <p>The second group of diabetes which existed before pregnancy can be split up into these classes:</p> <ul style="list-style-type: none">• Class B: onset at age 20 or older or with duration of less than 10 years• Class C: onset at age 10-19 or duration of 10–19 years• Class D: onset before age 10 or duration greater than 20 years• Class E: overt diabetes mellitus with calcified pelvic vessels• Class F: diabetic nephropathy• *Class R: proliferative retinopathy• *Class RF: retinopathy and nephropathy• *Class H: ischemic heart disease• *Class T: prior kidney transplant <p>An early age of onset or long-standing disease comes with greater risks.</p> <p>* Classes added or further subdivided after 1949.</p>

White P: Pregnancy Complicating Diabetes. *American Journal of Medicine* 1949, Nov. 1949:609-616.

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2.2 Methods

The project method is a non-systematic literature review searching the databases PubMed, McMaster PLUS and Cochrane library. The search was limited to original articles and reviews published in English. Search words: diabetes, pregnan*, risk, future, treatment.

PubMed was primarily used for the literature searches. When using the words 'diabetes pregnancy risk' and limited the search to links to full text, or free full text, humans, clinical trial, randomized controlled trial and English, 90 hits came up.

To find illustrations google was a useful tool.

The project is limited to deal with topics that are only/mostly found in pregnancies complicated with diabetes and their offspring, e.g. the topics that concern all newborns are let out, like breast feeding, mother-child bonding etc. Discussion of which insulin analog or other medications are preferred or recommended have also deliberately been let out.

2.3 Epidemiology

According to WHO [8] 346 million people worldwide have diabetes, and more than 80% of people with diabetes live in low- or middle- income countries. It is expected that by 2030 the number of people living with diabetes will double, and the increase in number will mainly affect developing countries [9].

In 2002, 1.4 % (776 out of 55 400) of women giving birth in Norway had diagnosed diabetes. Out of these 43% (330/776) had pregestational diabetes. The incidence of T2D- [7] and Gestational Diabetes Mellitus (GDM) is steadily increasing [10]. T2D is often undiagnosed at time of conception, and this increases the risk of diabetes related complications in pregnancy [7].

The reasons why we see more T2D in Norway today than previously is that ethnic Norwegian women are more overweight than before, and the number of immigrants from areas where T2D has high prevalence has increased. Amongst pregnant women from Pakistan approximately 30-50 % either has T2D or GDM [7].

2.4 Etiology and pathogenesis

Diabetes is mainly divided into two major groups, T1D and T2D, but with several subgroups who more-or-less fall into one of the main groups.

T1D is characterized by selective autoimmune destruction of the β -cells in the pancreatic Langerhans Islets, leading to hypoinsulinemia. T2D on the other hand is characterized by insulin resistance in body tissue, followed by uncompensated insulin production, a so-called 'relative insulin insufficiency' [11].

Of all patients with diabetes, approximately 10% have T1D, and 80-90% have T2D. The obvious discrepancy between these numbers harbor an undiagnosed group with T2D. Previously, T1D was referred to as 'childhood onset diabetes' and T2D as 'adult onset diabetes', but with the changes brought upon a modernized, technological society, we have developed into a more sedentary lifestyle with an energy surplus resulting in increased obesity and 'lifestyle-diseases'. This has led to a change in diabetic epidemiology and etiology, with both an increase in the number of T2D cases, and younger age at the time of diagnosis. This has been called the 'diabesity' epidemic [12].

Even though the cause of the diseases are different, the long term complications of all types of diabetes are the same, with secondary affection of multiple organ systems, especially the kidneys, eyes, nerves and blood vessels [12].

2.4.1 Pathogenesis of Type 2 Diabetes Mellitus:

The exact pathogenesis of T2D is still unknown, but there is a consensus that it is caused by both environmental and genetic factors. There is no linkage between auto-immunity and T2D, but there has been found several 'diabetogenic' genes that seem to play a role, in addition to lifestyle factors, such as level of activity, dietary habits and obesity. The two main characteristics of T2D are: 1) decreased ability of peripheral tissue to respond to insulin (insulin resistance) and 2) unsatisfactory compensation of insulin production in response to the increased demand due to insulin resistance [12].

Studies have shown an inverse correlation between free fatty acids (FFAs) and insulin resistance. Obese persons tend to have an abundance of FFAs, which in turn works as inhibitors of insulin signaling, resulting in decreased insulin sensitivity [12].

Adipose tissue is not only a storage organ, but it also has regulatory functions of the metabolism. Several adipocytokines that are involved in insulin sensitivity in peripheral tissues have been identified. Among these are leptin, adiponectin and resistin. Disturbances in these proteins are associated with insulin resistance and have been seen in obese persons [12].

2.4.2 Pathogenesis of gestational diabetes:

GDM is diabetes diagnosed during pregnancy that is not clearly overt diabetes [13]. It usually develops in second trimester and resolves post partum, but follow up of the condition is crucial, to avoid missing an undiagnosed T2D [14].

In pregnancies, the normal physiologic response to increased concentration of pregnancy hormones - including estrogens and progestins- is a reduction of fasting blood glucose, increased adipose tissue, delay in gastric emptying and increased appetite. As the pregnancy goes on, the woman will develop a reduced insulin sensitivity, and blood glucose levels will increase again. As seen similarly in T2D, this state will demand an increase in β -cell production of insulin [14]. It is not fully understood why women who develop GDM are not able to increase their insulin production in response to the increased insulin resistance. There have been suggested disturbances in the insulin signaling cascade [15], dysfunctional insulin receptor [16] in addition to a genetic predisposition. 66 genes have been found upregulated in placentas of women with GDM [17].

2.5 Diagnosing diabetes:

WHO has defined diabetes as a condition with fasting blood glucose ≥ 7.0 mmol/L, or a 2 hr plasma glucose ≥ 11.0 mmol/L. This definition was last reviewed November 2005. [18]. In 2011, WHO also recommended to test HbA1c for diagnosing diabetes mellitus. This test has shown to have a higher predictive value of microvascular complications. HbA1c value at 6.5% is recommended as cut-off point, but a value below this does not rule out diabetes. At the moment there is not sufficiently data to make any recommendations regarding HbA1c below 6.5% [19].

Table 2: Diagnostic criterias diabetes.

Diabetes	Venous plasma	Capillary blood
Fasting	≥ 7.0 mmol/L	≥ 6.1 mmol/L
120 mins oral glucose tolerance test (OGTT)	≥ 11.1 mmol/L	≥ 11.1 mmol/L
HbA1c	$\geq 6.5\%$	$\geq 6.5\%$

WHO: Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia- Report of a WHO/IDF consultation. 2006.

Table 3: Diagnostic criterias impaired glucose tolerance.

Impaired glucose tolerance	Venous plasma	Caillary blood
120 mins oral glucose tolerance test (OGTT)	$\geq 7.8 - < 11.1$ mmol/L	$\geq 7.8 - < 11.1$ mmol/L

WHO: Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia- Report of a WHO/IDF consultation. 2006.

The OGTT test should be performed as described by WHO [18], using a glucose load containing the equivalent of 75 g glucose dissolved in water or 1,75 g/kg of body weight to a maximum of 65 g.

To further distinguish the diabetes between type 1 and type 2 it is advised to measure diabetes associated auto-antibodies [20].

In Denmark they recommend screening for GDM early in pregnancy if the mother has high risk of GDM (previously GDM, glucoseuria and must have two out of three of: family history of diabetes, BMI > 27 , previous birth to macrosomic or LGA baby) [21]. In 28th -32nd gestational week they screen women with one out of the three risk factors

above, or women who were screened early in pregnancy, but then not diagnosed with diabetes [21].

The recommendations for screening in Norway is a bit different from Denmark since they divide the women with high risk of GDM into three different groups.

Table 4: Indications for glucose screening in pregnancy- Norway

Group A	<ol style="list-style-type: none"> 1. Previously gestational diabetes mellitus. 2. Family history of type 1- or type 2- diabetes in first degree relative. 3. Immigrants, especially from North Africa and Indian subcontinent, others by consideration. 4. Age >35. 5. Obese /overweight (BMI >27). 	As early in the pregnancy as possible. To be repeated in week 28- 30 if negative test the first time.
Group B	Manifest glucoseuria, especially if it is reproducible and without overt explanation	When glucoseuria is first detected. If first oral glucose tolerance test (OGTT) is negative, and glucoseuria is again detected, repeat test in 4-6 weeks (or sooner if in last trimester).
Group C	Development of polyhydramnion and /or rapid fetal growth in current pregnancy. Previous birth to large for gestational age baby or (>4500 g) or fasting blood sugar between 6.1 and 7.0 mmol/l.	OGTT by consideration. Also for women with previous congenital malformations or stillbirths.

Modified from Norwegian Society for Gynecology (<http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/veileder-i-fodselsjelp-2008/kapittel-8-diabetes-i-svangerskapet/>)

The Hyperglycemia and Adverse Pregnancy Outcome study (HAPO) [22] showed a strong association between maternal hyperglycemia and adverse pregnancy outcomes, even in the subclinical ranges. On behalf of this, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [23] has suggested new criterias for GDM. They are somehow 'stricter' with fasting plasma glucose (FPG) ≥ 5.1 mmol/l or 2 hrs plasma glucose after oral glucose tolerance test (OGTT) ≥ 8.5 mmol/l.

The WHO criterias are still being used in Norway, but in the Stork Grorud project they diagnosed the study participants both according to the WHO and the IADPSG criterias. Not suprisingly, the prevalence differed, with 13% with WHO and 31.5% with modified IADPSG criterias [24]. They also saw that this increase in prevalence was strongly associated with South Asian origin and pre-pregnant overweight.

2.5.1 Risk factors of developing gestational diabetes:

GDM is complex, and there have been found many risk factors for developing the condition. So far these factors are known:

- previous gestational diabetes
- obesity (BMI >30) or overweight (BMI 25-29)
- macrosomic infant in previous pregnancy
- suspected glucose intolerance in previous pregnancy
- glucosuria
- strong first degree family history of T2D or gestational diabetes
- history of unexplained fetal demise
- >24 years old

Women older than 24 years of age have a 7-10 times higher risk of developing gestational diabetes than younger women. Studies also show that obese women have more than 3-fold increased risk of gestational diabetes compared with non-obese women [14].

The STORK Gørudalen study also showed that genetics is an important factor in developing GDM [24].

Studies have shown that prenatal exercise can delay or prevent the development of GDM, and exercise during pregnancy can prevent complications to the baby [25]. Zhang et al. found that women who did not do any vigorous activity and spent 20 hrs or more each week watching television had a higher risk of developing GDM than women who did physical activity and spent less than 2 hrs each week watching television [25].

2.6 Diabetes and risk factors in pregnancy

Well-known complications and adverse outcomes of pregnancies complicated by diabetes are pre-eclampsia, preterm birth, fetal hypoxia, perinatal death, stilldeath, infant death, non-spontaneous start of labour, increased rate of caesarean sections, macrosomia or large for gestational age [14, 26-30]. Later in life the offspring of parents with T1D has an increased risk of developing T1D, seven fold increase if the mother has the condition [31, 32], and as much as 21 fold increase if it comes from the father [33]. GDM increases the risk of childhood obesity, T2D and metabolic syndrome at a very early age for the offspring [34].

2.6.1 Congenital malformations due to hyperglycemia

Several studies have shown an association between diabetes and congenital malformations in the offspring. The most commonly seen are neural tube- and cardiovascular defects [35-37]. Since these organ systems are developed within the eight gestational week, the influence of the maternal diabetes happens in this first period of the pregnancy. By this time, many women are not even aware of the fact that they are pregnant, so this reinforces the need for pre-conceptional diabetic care. This applies to women with pregestational diabetes, since GDM usually develops in second or third trimester [14], when the organogenesis is already completed.

Many recent studies have shown a link between pre-pregnancy obesity and congenital malformations [38-40]. This may be because many patients with T2D are undiagnosed, and are not discovered until later in pregnancy or later in life [41]. Since the prevalence of T2D is rising, it is expected to see an increase in diabetes associated congenital malformations [4]. This is a massive challenge for the health care, and rises the question of whether it is indicated to screen larger groups for diabetes.

Eidem et al. [30] conducted a large population based study where they linked the Medical Birth Registry of Norway (MBRN) and the Norwegian Childhood Diabetes Registry (NCDR). They looked at all births in Norway from 1999 to 2004 (N=350 961). Of these were 1583 births by women with pregestational T1D. The prevalence of congenital malformations in the diabetes group were 5.7% compared to 2.9% in the rest of the population. The most commonly seen malformation in this study was affects of the cardiovascular system; it was seen three times more often than in the background population.

Eidem et al. [30] reported no association between duration of diabetes and adverse outcome after adjusting for maternal age and year of birth. However, they did see that the T1D group was not heterogeneous, and the risk was different in different socioeconomic groups. The women with college or university education and T1D 'had a borderline significant lower proportion compared to those with high school education only (adjusted odds ratio 0.58, 95% CI 0.31-1.07, global p-value for education level: 0.09)' [30].

‘Women in the diabetes group who reported smoking, had an adjusted odds ratio for malformations of 1.36 (0.79-2.3) compared with those who did not report smoking’ [30]. In this context it is interesting to notice that more women in the diabetes group reported smoking during pregnancy, and fewer had college- or university degrees than in the background population.

The Confidential Enquiry into Maternal and Child Health (CEMACH) [42] from UK had similar findings. The prevalence of congenital malformations were doubled compared with the background population (41.8/1000 compared with 21/1000).

A cohort study done by Temple et al. in 2006 [43] had amazing results concerning prepregnancy care in women with T1D. The women in the prepregnancy care had lower HbA1c before conception and the two first trimesters, and they found fewer congenital malformations, stillbirths, neonatal births and very premature deliveries. They did not, however, see any differences concerning pre-eclampsia, glycemic control in late pregnancy, macrosomia and caesarean section.

Several studies report hypertrophic cardiomyopathy in newborn infants of mothers with T1D [44-46]. Most of these changes were asymptomatic and disappeared within the first six months of life, but some lead to severe morbidity and mortality.

Usually the majority of the infants only need supportive care, and postnatal echocardiography is not required unless there are clinical signs [47].

During labour it was found that ST depression occurred more frequently in pregnancies complicated by diabetes, and especially in pregnancies with poor glycemic control in late pregnancy [48].

Brain natriuretic peptide (BNP) is a peptide produced in the cardiac muscle if put under mechanical stretch, and it works in the regulation of extracellular volume and blood pressure by increasing natriuresis, and inhibiting the renin-angiotensin-aldosterone axis. In the fetus it works as a vasodilator in the placental circulation and probably has protective autocrine effects by inhibiting fibrosis and hypertrophy of the heart [49]. Increased plasma concentrations of BNP and proBNP are seen in patients with heart failure, children with congenital heart disease and newborns with severe fetal distress [50, 51].

It has been seen higher median plasma proBNP concentrations in offspring of women with suboptimal glycemic control (HbA1c >6.2%) compared with offspring of healthy women [26].

A study by Russels et al. [100] also reported increased levels of BNP and proBNP in the umbilical cord blood of offspring from women with T1D and the increase was mostly marked in infants of women with poor glycemic control in early pregnancy.

Another complication that can be seen is placental insufficiency, leading to intrauterine growth restriction and a baby who is small for gestational age (SGA) [54].

This has major implications especially if the baby is born pre-term. The SGA baby is known to have increased risk of neurodevelopmental sequelae [55] and persistent hypoglycemia postnatally. However, studies have shown that this outcome may be prevented by well-controlled diabetes in pregnancy [56, 57].

2.6.2 Death of fetus/ infant:

In different literature there are many different terms to describe death of a fetus or child, such as fetal death, fetal demise, in utero loss, intrauterine (fetal) death, stillbirth, (early) neonatal death, perinatal death and infant death. Therefore there is a need to clarify the understanding of the terms used in the following section.

Table 5: Definitions of terms to describe death of a fetus or child

	Definition
Stillbirth	In utero loss delivering after 24 completed weeks of gestation
Perinatal death	Stillbirth or death during the first 7 days of life
Early neonatal death	Death of a live born infant during the first 7 days of life
Neonatal death	Death of a live born infant during the first 28 days of life
Infant death	Death during the first year of life

Adapted from Eidem 2011 and CEMACH.

Table 6: Comparing data on pregnancy outcome, studies from Norway and Denmark

	Eidems study 1)	Jensen's study 2)
Study period	1985-2004	1993-1999
Country of origin	Norway (nationwide)	Denmark (selected centres)
Participants (n)	1 161 092	70 089
Diagnosis	T1D	T1D
Participants with diabetes (n)	1 307	1218
Risk of perinatal death and stillbirth	x3*	x 4* (Perinatal mortality only)
Risk of stillbirth	-	x 5*
Risk of infant death	x2*	-
Risk of stillbirth and infant death	x3*	-
OR stillbirth	1.8 (95% CI 1.2-2.8)	-
OR perinatal death	1.6 (95% CI 1.1-2.3)	-
OR stillbirth or infant death	1.6 (95% CI 1.1-2.2)	-

(* compared with background population.)

1) Eidem et al. Diabetologia 2011: Perinatal and infant mortality in term and preterm births among women with type 1 diabetes.

2) Jensen et al. Diabetes Care 2004: Outcomes in type 1 diabetic pregnancies.

As we can see from the table above, Eidem [30] found a lower risk of perinatal death and stillbirth compared with Jensen's study [101]. This might be due to differences in the population sizes and selection of centres included in the Danish study. Another unknown factor which may play a role in the outcome, is the potential event of undiagnosed T2D in the background population. The screening for diabetes in Norway is not as systematic as in other comparable countries.

The different results may also reflect different national differences as genetics, standard of health care, socioeconomic status etc.

Both Eidem [30] and Jensen [101] confirmed that preterm deliveries occur much more frequently in pregnancies complicated by diabetes, but most interestingly, Eidems study adjusted the numbers for perinatal death into pre-term and term deliveries. And even

though pre-term delivery plays a huge role in perinatal deaths, their findings showed that the excess rate of perinatal death was confined to the term T1D group. There was an insignificant difference in mortality rates in preterm deliveries in the two groups.

Eidems study [30] found that mothers of T1D were on average slightly younger at delivery and had slightly lower parity than those without T1D, and they were more often of European origin. Other differences were minor. Of the women with T1D, almost 20% were registered with pre-eclampsia, 26% delivered preterm, out of which 42% were spontaneous pre-term deliveries. Median gestational age for the women with T1D were 38.4 weeks compared with 40.2 weeks in the background population.

Of the women who delivered pre-term, there were no differences in the risk of perinatal death between women with T1D and the background population. However, in the group of women with T1D who delivered spontaneously at term there was a five times higher risk of perinatal death than in the background population.

Another interesting finding of Eidem et al. [30] were that the offspring of women with T1D had a significantly higher risk of death during the first year of life compared with the background population.

Another Danish study reported that 50% of stillbirths were unexplained, but most of these had suboptimal glycemic control in late pregnancy, many also had problems with diabetic nephropathy, smoking and low social status [58].

The explained stillbirths were pregnancies complicated by intrauterine growth restriction, pre-eclampsia, umbilical cord problems, acute asphyxia, placental abruption, intrauterine infection, congenital malformations or maternal ketoacidosis. Many were also related to diabetes, for example, due to congenital malformations, diabetic nephropathy and maternal diabetic ketoacidosis [26].

Other characteristics of pregnancies ending with a stillbirth were smoking and a low social status [58].

There has been suggested that oxidative stress could play a role in pre-eclampsia, and that the supplementation of vitamin C and E could reduce the incidence of this serious disorder [59, 60]. Randomised placebo-controlled trials [59, 60] have been done to further investigate this, and the women were either given 1000 mg vitamin C and 400 IU vitamin E daily, or a placebo. The supplementation did not prevent pre-eclampsia in women with increased clinical risk factors for pre-eclampsia [59] or in women with T1D [60].

In pregnancies with GDM there is no increased risk of perinatal death or stillbirth, but the incidence of macrosomia and large for gestational age (LGA) is much higher than in the general population [61]. Later in life, the offspring has an increased risk of developing T2D [14].

2.6.3 Sum up of outcomes of risk factors

Table 7: Maternal hyperglycemia in different stages of the pregnancy represents risk factors for different pregnancy outcome, divided in pregestational diabetes and gestational diabetes

Hyperglycemia	Risk factor	Pregestational diabetes	Gestational diabetes
First trimester	Congenital malformations	*	
Third trimester	Pre-eclampsia	*	
Third trimester	Preterm birth	*	
Third trimester	Perinatal death/ stillbirth/ infant death	*	
Third trimester	Macrosomia/Large for gestational age	*	*

*: increased risk

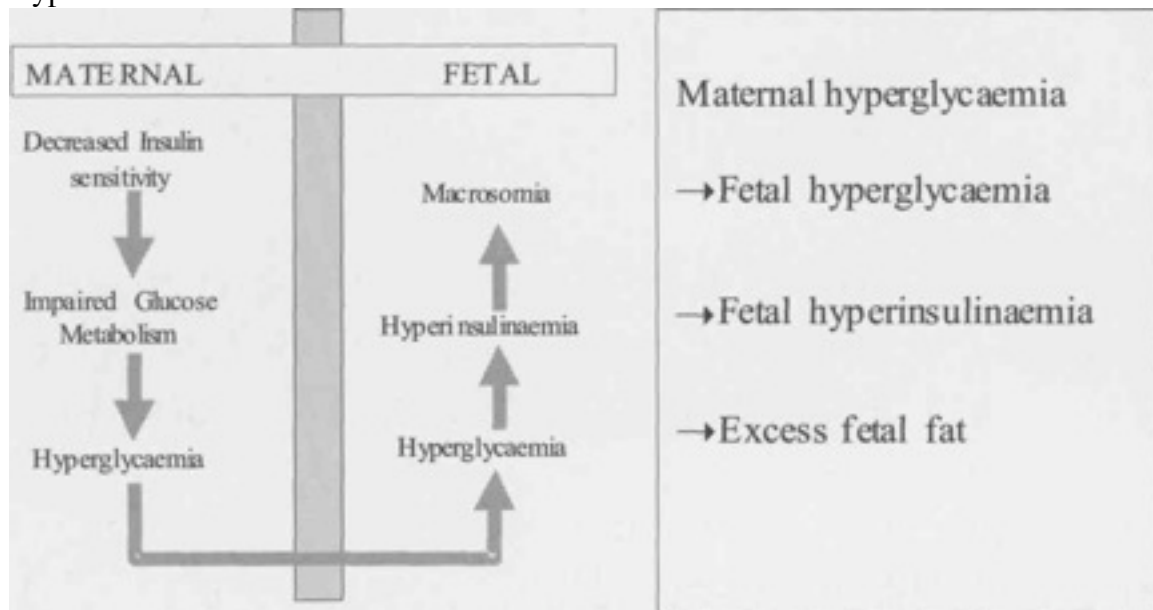
2.6.4 Teratogenicity and fetal effects of hyperglycemia:

Insulin is not transported across the placenta [4, 28], and the fetal pancreatic beta cells are not present until 10th gestational week [62], so it can not be responsible for any congenital malformations associated with pregestational diabetes. The teratogenic effect of hyperglycemia, on the other hand, has been proved by animal studies [63]. In the first trimester the natural physiologic response of pregnancy is a hypoglycemic state in healthy pregnancies, the potential teratogenic effect of glucose (hyperglycemia) applies to women with pregestational diabetes.

Hypoglycemic episodes have proven embryotoxic in animal studies, but this has not been seen in humans [64, 65].

The fetal effect of maternal hyperglycemia has been explained in the Pedersen hypothesis [22, 26]. It states that maternal hyperglycemia gives a fetal hyperglycemia, which causes a fetal hyperinsulinemia through overstimulation of the fetal beta-cells. Since insulin is an anabolic hormone this will stimulate protein, lipid and glycogen [28], and cause increased fetal growth, more adipose tissue and increased hepatic glycogen storage [26]. This increase in metabolism will be manifest as LGA or macrosomia and it may cause relative decrease in arterial oxygen content [26]. The association between hyperglycemia and hyperinsulinemia and hypoxia have been seen in animal studies [26].

Figure 1: The fetal effect of maternal hyperglycemia explained by The Pedersen Hypothesis:



Michael Varner, lecture on Gestational Diabetes, University of Utah Health Services Centre, [66])

Pregnancies complicated by diabetes, pre-eclampsia and fetuses small or large for gestational age show an increase in stillbirths and fetuses with sign of hypoxia, acidosis, increased plasma and amniotic fluid values of erythropoietin (EPO) [67, 68]. It is known that the major stimulus of EPO is hypoxia. There have been described increased levels of amniotic values of EPO prior to stillbirth in pregnancies complicated by diabetes [69].

After birth the infant will no longer receive placental nutrition, and fully depend on its own glucose- and ketone bodies- production. The Pedersen hypothesis indicate how the baby is at risk of hyperinsulinism, and therefore will have little glucose available as fuel. The baby will be in a state of hepatic glycogen- and lipid production, and will not produce ketone bodies [28]. This state of hypoketonaemic hypoglycemia is potentially neurotoxic, but there is no evidence that it will occur without clinical signs [28]. Since there are no clinical studies with sufficient evidence to prove the link between neonatal hypoglycemia and brain injury, it has not been possible to provide evidence based guidelines [28]. However, guidelines for the prevention and management of neonatal hypoglycemia due to maternal diabetes have been developed, and are being used [70].

Another response of the fetus to the maternal hyperglycemia is increased growth, either classified as macrosomia or LGA [28]. These are not interchangeable terms. Macrosomia means a baby with a birth weight higher what was genetically determined, and it is defined as a birth weight above the 90th percentile. This usually means increased growth of abdominal fat and organs. , LGA refers to a fetus or infant who is larger than expected for the age and gender or with a birth weight above the 90th percentile.

The measurement is based on the estimated gestational age of the fetus or infant, compared with what is considered normal height, weight, head size, and developmental level for a fetus or infant of the same age and gender [28].

In women with GDM it has been shown that increased mean maternal glucose concentration is associated with increased neonatal birthweight [54], and elevated insulin concentrations in fetal blood and amniotic fluid is associated with macrosomia [71, 72]. The two terms are often confused, but it is macrosomy and organomegaly that is mainly associated with diabetes in pregnancy [28].

Giving birth to a baby with macrosomia or LGA may lead to complications, such as shoulder dystocia, obstructed labour, perinatal hypoxia-ischemia and birth related injuries in both mother and baby [14, 28]. To avoid complications in labour, it is often preferred to deliver by cesarean section when a macrosomic or LGA baby is expected [14].

National cohort studies in the UK and Netherlands found that the rate of cesarean section in women with diabetes (43% and 44%) was more than doubled compared with the rest of the UK population (20%) [28]. But use of caesarean section involves trauma to the mother, and the cost vs. benefits have to be taken into consideration when electing mode of delivery [28].

The Hyperglycemia and Adverse Pregnancy Outcome [22] study from 2008 found that even subclinical hyperglycemia was significantly associated with LGA births.

Clausen et al. concluded in their study from 2008 [73] that a hyperglycemic intrauterine environment is involved in the pathogenesis of T2D or pre-diabetes in the adult offspring of mothers who had diet treated GDM or T1D during pregnancy. The study was Danish and most of the participants were of Caucasian origin.

2.6.5 Maternal effects

It is more difficult to maintain stable blood sugar levels during pregnancy because of the change in metabolism and the influence of the hormones [14]. This fluctuation in blood glucose may deteriorate microvascular complications [27], and it is therefore very important that the woman with pregestational diabetes will seek medical help and intervention before getting pregnant.

To optimize the outcome for the fetus, it is important that the blood glucose is within the desired range, and this may demand upjusting the insulin doses. However, a sudden improvement in glycemic control with increased insulin treatment, may temporarily deteriorate retinopathy [74, 75]. It has been shown that poor glycemic control and

hypertension in first trimester increases the risk of progression [76]. In addition to maintaining stable blood sugars, the retinas need to be investigated before and during pregnancy, and if necessary laser treatment can be given [27].

The major obstacle to achieving tight glycemic control in pregnant women is the risk of hypoglycemia. The risk is highest in first trimester, especially between 8th and 16th gestational week [77-79]. The risk is as much as five times higher than the year before getting pregnant [78]. Hypoglycemia may lead to severe incidents, like hypoglycemic coma [80], traffic accidents [77] and death [81]. To avoid hypoglycemia continuous blood glucose monitoring is recommended in pregnancy [82].

New-onset hypertension or pre-eclampsia are relatively common and potentially serious complications of pregnancy. The incidence of hypertension in women who have diabetes is 15-20 % compared with 5% in the background population [83, 84].

Several factors contribute in the development of hypertension, and it is unclear what comes first. Several observational studies have shown a link between the development of hypertension in pregnancy hyperinsulinemia and insulin resistance [85-87]. Insulin does promote weight gain, which may increase blood pressure [27]. However, there has not been found that changes in blood pressure is associated with the use of exogenous insulin [27].

There seems to be a 'vicious cycle' between hypertension and nephropathy where the presence of one of them both increases the risk of and deteriorate the presence of the other [88, 89]. The development of nephropathy in patients with diabetes heralds an increased risk of mortality not only from end-stage renal failure, but also from cardiovascular causes [90].

The presence of microalbuminuria or nephropathy in early pregnancy is associated with increased risk of preterm delivery, mainly due to pre-eclampsia [91].

For women with GDM the main long term concern is the increased risk for developing metabolic syndrome and T2D. A review study by Vohr and Boney in 2008 [92] found strong evidence that women with GDM and obesity have a much higher risk of developing metabolic syndrome than women without GDM.

2.7 Treatment and standard of care

All the literature reviewed for this project emphasized the importance of planned pregnancy for women with diabetes. The subject must be brought up in relatively early age, and the women must use a safe contraception method. The National Clinical Guidelines [7] from The Norwegian Directorate of Health recommends that HbA1c should be <7% by the time on conception and through first trimester. In second and third trimester HbA1c should be below 5.8%. Keep in mind then that from second trimester this is normally 1%-point lower than when not pregnant.

The Norwegian Directorate of Health: Guidelines for planned pregnancy for women with diabetes [7]:

- Consider referral to specialist health care if preconceptional plasma glucose (PG) is not achieved in desired range. During pregnancy, all women with diabetes should be followed by units experienced in the field.
- Motivate to achieve optimal regulation of diabetes.
- Discontinue per oral antidiabetic treatment if this is being used. Metformin may be used. Consider starting insulin treatment.
- Discontinue statins, ACE- inhibitors and angiotensin II- antagonists.
- Optimize blood glucose control. Refer to dietician if needed.
- If hypertension is present she must be referred to specialist health care.
- Motivate to stop smoking
- Consider referring to ophthalmologist.
- Intensify patient education.
- Start taking folic acid and omega-3 fish liver oil daily.

During pregnancy the aim is to keep PG between 4 and 8 mmol/l throughout the whole day and night.

Women diagnosed with GDM are given diet and exercise counseling. If needed they also have to start continuous blood glucose monitoring and insulin therapy. They are generally given the same advices as other pregnant women when it comes to daily caloric intake, vitamin supplements and exercise. All pregnant women in Norway are recommended to take 400 µg folic acid and omega-3 fish oil daily [93].

It is recommended to do an OGTT on women with GDM 6-12 weeks after birth, since not all GDM resolve after birth but remains as T2D [7].

Mathiesen's recommendations are in concurrence with the Norwegian. During pregnancy she recommends that preprandial PG should be between 3.5 and 5.9 mmol/l, and postprandial PG should be between 3.5 and 7.8 mmol/l [27].

To avoid hypoglycemia is a challenge, so insulin dose should be reduced at around 8-16 week, and steady increased again from 16th week until delivery [27]. In second and third

trimester the American Diabetes Association (ADA) has recommended an HbA1c <6% [94].

The Norwegian Society for Gynecology [10] recommends that if HbA1c is >8 % periconceptional, the women should be offered early ultrasound (at about 12th gestational week) in concern of congenital malformations.

In Copenhagen, Denmark, women with pregestational diabetes are offered antenatal ultrasound examination of fetal growth rate at 28, 34 and 37 weeks, once weekly non-stress testing from 33 to 34 weeks and kick counting from 28th week until delivery [26]. This strategy, in addition to strict glycemic control has given the result that the stillbirthrate in the diabetes group is closer to the background population [26].

There is no international consensus regarding the recommendations for when to initiate time of delivery in pregnancies complicated by diabetes. The National Institute for Health and Clinical Excellence (NICE) [95] says they should be offered elective birth after 38 completed weeks, ADA states that 'well-monitored diabetic women achieving excellent glycaemic control without obstetrical complications can await spontaneous labour up to 39-40 weeks gestation' [94]. The recommendation by the Norwegian Society for Gynecology (NGF) for women treated with insulin is induction around term, others should be considered individually. Ceasarean section should be used in obstetric complications and if serious vascular, kidney or eye-complications [10].

After delivery it is very important that the newborn will be monitored closely, especially concerning the glucose levels, since it is at high risk of hypoketonaemic hypoglycemia [27, 28].

3.0 Discussion

Women in Norway with pregestational diabetes are being closely followed up, and given pregestational care and information. This is also the group with highest risk of adverse outcome, in the form of hypoglycemic episodes, congenital malformations in infant, preterm deliveries, pre-eclampsia, stillbirth, perinatal death and infant death and macrosomia and LGA. In addition to complications directly connected with pregnancy, the mother has increased risk of microvascular complications due to the general hyperglycemia. But despite this awareness and massive health care service, the incidence of adverse outcome in pregnancies complicated by diabetes is still high. Since both T2D and GDM is on the rise, the situation is not expected to change in the future, unless changes are being made.

Eidems study on congenital malformations found that the risk of congenital malformations were doubled and the risk of cardiovascular malformations were tripled in the T1D group compared with the background population. Their findings indicated that the women are not satisfactory regulated, and improvements can be made.. The underlying mechanisms to the congenital malformations are not fully known, but hyperglycemia induced oxidative stress and glyco-oxidative mechanisms have been suggested to play an important role [30]. Cigarette smoking and socioeconomic background as contributing risk factors to congenital malformations should also be investigated further.

As strict glycemic control before conception and in first trimester will reduce the risk of congenital malformations, it is likely that glycemic control in second and third trimester will reduce the rate of stillbirths, perinatal death, complicated deliveries and caesarean sections, macrosomia and LGA.

It is also advisable to motivate the women to refrain from smoking during pregnancy.

Antihypertensive treatment in pregnancy is complicated as some of the most commonly used medications are contraindicated in pregnancy. However, there is strong evidence that proper hypertensive management in women with microalbuminuria or diabetic nephropathy will reduce the risk of pre-eclampsia and pre-term delivery [91, 96].

The main challenge for improving the outcome for pregnancies complicated by diabetes is to maintain plasma glucose within desired range. There exists a massive amount of literature supporting the benefit of avoiding hypoglycemia, but very little has been said about the reasons why this is not achieved in all women. Is it a motivational problem in the women with diabetes? Are the health service providers not putting enough emphasis on the importance of maintaining strict glucose control, or is it a communicative problem? There would be helpful to investigate this problem more, and come up with strategies or guidelines to motivate these women even more.

In many countries -another obstacle to maintain strict glucose control is the cost. Not only does it demand a lot of effort from all of the implied persons, but it also demands a lot of equipment and medications. This should however not be the situation in Norway as treatment of diabetes is free for the patient. All medical expences related to the disease are paid by the government.

There is also an ethical side that arises with parts of the treatment today. Many clinics offer the women early ultrasound examination [26]. This is in concern of congenital malformations. If a malformation is detected on early ultrasound, the next step is for the woman to choose between an elective abortion or to let the pregnancy move on and deliver the baby.

In Norway today, there is an ongoing debate on whether early ultrasound in pregnancy should be offered by the public healthcare to all women. One of the arguments against this proposal is that we might get a 'selective society' where there is no room for people with disabilities. The choice of raising a child with malformations will always be a difficult decision for the woman.

There has been suggested new criterias for diagnosing GDM [23], and as seen in Jenum's study from 2012 [24], this will lead to a significant increase in the prevalence of GDM. The benefits of using the new criterias are to prevent macrosomia in offspring, childhood overweight and metabolic factors that may increase the risk of cardiovascular disease [23]. On the other hand, to recommend this new standard will have a large impact on the health care budget. When considered the poor reproducibility of the OGT-test [97-99], the cost vs. benefit is large. Jenum suggests that population- based strategies to prevent overweight and improve living condition earlier in life may be more beneficial.

4.0 Conclusion

There are still many challenges in the pregnancy care of women with diabetes. One is to make sure that women with already diagnosed diabetes (T1D and T2D) are taken care of in prenatal diabetic clinics which are updated on national and international treatment guidelines. This diabetes care has to include pre-pregnancy care. The second challenge will be to find the women with unknown T2D and the women in risk of developing GDM.

The main goal will then be to achieve a glycemic control as close to normal as possible while avoiding severe hypoglycemia as well as frequent moderate hypoglycemia. To achieve this goal is a huge challenge that has not yet been met. Little has been documented in concern to motivational interviews and there might be a potential for improvement here. Also the technology for glucose monitoring and insulin administration available today may need evaluating for potential improvements.

Hypertension in pregnancy is common, but still not optimally treated. The impacts of hypertension are massive, and this must be a field of improvement in the future.

The outmost desirable scenario for the future would be to reduce the incidence of new onset T2D and GDM to a minimum. Some of the triggering factors are well known, as overweight/obesity and sedate lifestyle. This also triggers other diseases, so there is no doubt that a general alteration from sedate to active lifestyle would be beneficial for the whole society, and would be a very cost-efficient initiative.

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